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Familial Wilms' Tumor: A Descriptive Study

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Among 6,209 patients with Wilms' tumor entered on the National Wilms' Tumor Study (NWTS), 93 patients (1.5%) from 63 families had a positive family history. In 30 of these 63 families a (half) sibling or parent of the NWTS patient was confirmed to have had Wilms' tumor. Fifteen (16.1%) of the familial, but only 7.1% of sporadic cases, had bilateral disease. Mean ages at diagnosis were 15.8 vs. 35.2 months ($P = 0.012$) for bilateral vs. unilateral familial cases and 32.0 vs. 44.7 months for sporadic cases. Intralobar nephrogenic rests were found twice as frequently in association with the tumors of familial as with those of sporadic cases. Cases of bilateral and metastatic disease tended to cluster within specific families, suggesting heterogeneity in the genetic etiology. The number and age distribution of familial cases transmitted through the father were about the same as those of cases transmitted through the mother. This finding is inconsistent with models of genomic imprinting that involve familial transmission of a tumor-suppressor gene and it casts further doubt on the hypothesis that all bilateral cases are hereditary.

Key words: age at diagnosis, bilateral Wilms' tumor, genomic imprinting, intralobar nephrogenic rests

INTRODUCTION

Familial Wilms' tumor is rare, accounting for but a tiny fraction of cases of a disease that itself affects only 1 in every 10,000 children [1,2]. Estimates of the percentage of Wilms' tumor cases of familial origin range from 1 to 2.5%, depending on the completeness of ascertainment and whether distant relatives are considered [1,3,4]. Careful study of the scarce multiple case families has nonetheless contributed greatly to our understanding of carcinogenic mechanisms. Statistical analyses led Knudson and Strong [5] to extend to Wilms' tumor the two-stage mutational model that has guided much of our thinking about mechanisms during the past two decades [6]. Demonstration of a germinal *WT1* mutation and loss of the wild-type allele in a bilateral tumor confirmed the operation of the postulated two-hit mechanism at the molecular level [7]. A *WT1* mutation has been linked to the transmission of Wilms' tumor in at least one family [8]. Linkage analyses of other large Wilms' tumor families, however, suggested that another gene or genes were also involved in familial transmission [9–11]. There is increasing realization that Wilms' tumor is heterogeneous in terms of genetic etiology and pathogenesis [12,13].

Most studies of familial Wilms' tumor conducted heretofore have used pedigrees reported in the literature in order to garner sufficiently large sample sizes for meaningful statistical analysis [1,5,14]. Such reports are likely to be biased towards larger and more "interesting" families. An opportunity to study a large and relatively unselected sample was provided by the resources of the National Wilms' Tumor Study Group (NWTSG) [15]. In operation for over 25 years, the NWTSG has registered an estimated 70% or more of the total national U.S. incidence of Wilms' tumor since 1980 [16]. This paper reports the results of a descriptive study that contrasts the clinicopathologic and epidemiologic features of NWTSG patients having familial disease with those of patients having sporadic disease.

PATIENTS AND METHODS

Between October 1969 and June 1994, the NWTSG registered on study 6,520 patients under the age of 16 years at diagnosis of their Wilms' tumor, clear cell sarcoma, or rhabdoid tumor of kidney [17]. Baseline and follow-up data consisting of registration card, surgery and pathology checklists and narratives, radiation therapy records, and flow sheets were requested uniformly for all patients. The histologic subtype and, for cases registered

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since 1980, the presence of intralobar or perilobar nephrogenic rests were evaluated by the NWTSG pathology center [12,17]. Characteristic congenital anomalies were noted from registration, pathology, and surgery records as well as from a family questionnaire. The latter also provided information on parental age.

Possible cases of familial Wilms' tumor were identified from the registration card and family questionnaire, both of which specifically requested data on Wilms' tumors or other cancers in family members. Upon learning of such a case, a confirmation process was initiated that usually included requests to contact the patient's family for release of medical records and culminated in the receipt of the pathology report of the diagnosis of Wilms' tumor in a family member. Sometimes the family member identified as having a Wilms' tumor was also registered with the NWTSG, in which case confirmation was not needed. In a few instances involving families who had been the subject of published reports, confirmation was obtained by consultation with the author or the registering physician. The NWTSG patient was considered to have familial disease only if confirmation of a Wilms' tumor diagnosis was obtained for at least one family member.

Although information on age at diagnosis was available for most of the confirmed cases not registered with the NWTSG, and the bilaterality of the tumor was known for some, other details such as the histologic subtype and the presence of congenital anomalies were often lacking. In order to maintain uniformity in the information source and to avoid possible selection bias, therefore, the analysis of clinicopathologic and epidemiologic features was restricted to NWTSG patients. Information on the structure of the immediate family was available for most patients from the family questionnaire or from the family and medical history requested for those who survived 5 years and were enrolled in the NWTSG long term follow-up study [18]. Some further information on the extended family was collected during the process of confirmation. Several of the pedigrees were judged to be incomplete, however, and unsuitable for systematic study. Thus, the present report is limited to a simple descriptive comparison of familial vs. nonfamilial cases. More formal segregation and other genetic analysis will necessarily await completion of systematic interviews that have only recently been initiated.

Age distributions in various patient subgroups were estimated using a kernel smoother available in the S statistical language [19]. Evaluation of the statistical significance of age differences was based on t and F tests that are robust to moderate departures from Gaussian distributions. Survival differences were evaluated by the log rank test. Confidence limits and P values for odds ratios (OR) were based on "exact" statistical methods [20]. Intrafamilial clustering was evaluated using a likelihood ratio test based on the logistic-binomial model [21].

RESULTS

Histology, Stage, and Outcome

Ninety-three (1.4%) of the 6,520 NWTSG patients, from 63 separate families, were confirmed to have at least one family member with Wilms' tumor. None of the 93 familial cases had a diagnosis of clear cell sarcoma or rhabdoid tumor of the kidney, although 4.5 were expected based on the 311 such cases observed among 6,427 registrants without evidence of familial disease ($P = 0.02$). Three familial cases had diffuse anaplasia and one had focal anaplasia [22], which was close to the 4.4 and 1.3 cases expected, respectively, from the nonfamilial data. One patient with diffuse anaplasia had a sibling registered with the NWTSG with a diagnosis of nonanaplastic Wilms' tumor. Otherwise the histologic diagnoses for registered siblings were concordant and of "favorable histology." Subsequent analyses excluded the clear cell sarcomas and rhabdoid tumors of the kidney, leaving 6,116 sporadic cases as controls for comparison with the 93 familial cases.

Fifteen (16.1%) of the familial cases, but only 7.1% of the sporadic cases, had bilateral disease at diagnosis (14 cases) or subsequently (1 case): OR = 2.5; 95% confidence limits (CI) = 1.3 – 4.4; $P = 0.006$. Excluding those that were bilateral at onset and a few others, including one familial case, where the Wilms' tumor occurred in a solitary or horseshoe kidney, the stage distribution [15] for the familial cases was I 28%, II 26%, III 23%, and IV 23%. It was 36%, 26%, 24%, and 14% for the controls ($P = 0.05$). After adjustment for stage, the relapse-free survival (18 relapses observed vs. 18.2 expected, $P = 0.99$) and survival outcomes (13 deaths vs. 12.6 expected, $P = 0.88$) for the familial cases were almost exactly as expected from comparison with the sporadic cases.

Six of the 15 cases of bilateral disease clustered in three families, each having two such cases ($P = 0.05$). Restricting attention to the 78 patients from 57 families who had Stage I–IV disease at diagnosis, an analysis of variance treating stage as a "continuous" variable yielded an F ratio of $F_{56,21} = 2.37$ ($P = 0.016$), further suggesting that the stage distribution was not uniform across families. Seven of 18 patients with hematogenous metastasis at diagnosis (Stage IV) came from just three families, one having three such patients and the others two each ($P = 0.006$).

Age Distributions

Table I summarizes the age distributions for familial and sporadic cases. The latter were divided according to bilaterality of disease at onset and the familial cases both by bilaterality and according to whether transmission occurred through the mother or the father of the NWTSG case. (For 27 cases where the only confirmed family

TABLE I. Distribution of Age (in Months) at Diagnosis

Patient subgroup	No. of patients	Mean	Standard deviation	Median
Sporadic, unilateral	5675	44.7	31.8	39
Sporadic, bilateral	441	32.0	24.7	27
Familial	93	32.1	25.1	25
Familial, unilateral	78	35.2	24.9	29.5
Familial, bilateral	15	15.8	19.4	8
Familial, paternal[a]	31	35.8	28.4	27
Familial, maternal[b]	35	32.7	24.2	29
Familial, others[c]	27	27.0	22.1	21

[a]Transmission through father.
[b]Transmission through mother.
[c]Indeterminate transmission.

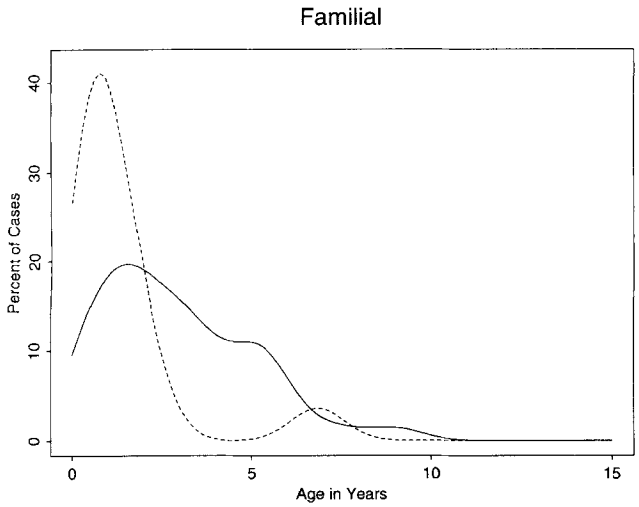

Fig. 1. Age-at-onset distributions for familial Wilms' tumor. Unbroken line, unilateral disease (n = 78); broken line, bilateral disease (n = 15).

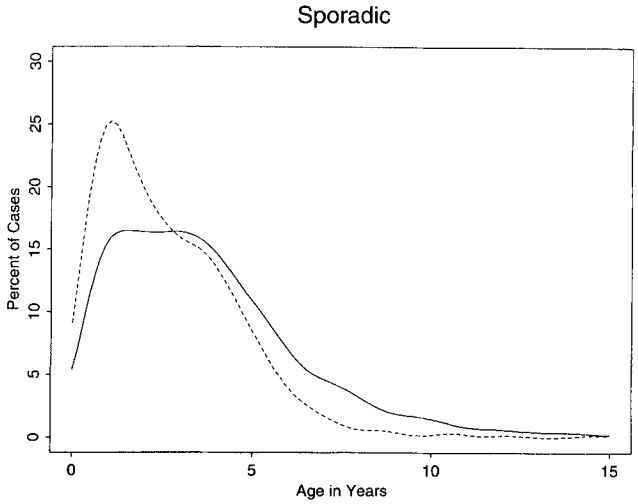

Fig. 2. Age-at-onset distributions for familial Wilms' tumor. Unbroken line, unilateral disease (n = 5,675); broken line, bilateral disease (n = 441.)

member with Wilms' tumor was a full sibling, the parent responsible for transmission could not be determined.) No difference in age was evident when patients were grouped according to parental transmission ($P = 0.41$). On the other hand, the difference in the age distributions between patients with unilateral vs. bilateral disease was just as striking for the familial (Fig. 1, $P = 0.012$) as it was for the sporadic cases (Fig. 2, $P \approx 0$). Among the four age distributions shown in Figures 1 and 2, the only two that were not significantly different from each other were the sporadic, bilateral and familial, unilateral distributions ($P = 0.29$). The slight suggestion ($F_{62,30} = 1.43$, $P = 0.14$) for intrafamilial correlation of age was entirely explained by the clustering of bilateral cases already noted: the F ratio was reduced to $F_{56,21} = 0.95$, $P = 0.58$ when unilateral cases only were considered.

Arithmetic mean ages of both fathers (30.7 vs. 29.2 years, $P = 0.03$) and mothers (27.6 vs. 26.3 years, $P = 0.03$) at patient birth were higher for the familial cases than for controls. The mean ages were particularly elevated among fathers (32.5) and mothers (28.9) of cases where the only confirmed family member was a sibling. This result is most likely an artifact, however, because family sizes are generally larger, and hence parents are older, when two or more sibs are known to have a particular diagnosis [4].

Degree of Relationship

Table II shows the distribution of the 63 families according to 1) the closest relationship involving an NWTSG patient and another confirmed case and 2) the total number of confirmed and probable cases in each family. Six families with at least one confirmed besides the index case had additional unconfirmed but probable cases of Wilms' tumor: one had five, one had two, and four had a single such case. There were 24 families with two cases registered with the NWTSG (11 sibling pairs; 3 half-siblings; 5 first cousins; 2 first cousins once removed; and 3 second cousins) and 3 with three NWTSG cases (one with two full and one half-siblings; one with two full sibs and a cousin; and one with three distantly related cases). The remaining 36 families had but a single NWTSG patient. Five families have been the subject of previous reports [9,11,23–27].

In four families the NWTSG patients had a twin. One dizygotic twin pair was concordant for Wilms' tumor. The other three co-twins, all monozygotic, have been followed without disease to ages 13–15 years and are thus quite unlikely to develop Wilms' tumor.

TABLE II. Degree of Closest Relation and Number of Affected Family Members in 63 Families With Multiple Cases of Wilms' Tumor

Closest relation[a]	No. of affected family members[b]								
	2	3	4	5	6	7	8	9	Total
Full sibling	15	3	2						20
Parent	7								7
Half-sibling	2			1					3
Aunt/uncle niece/nephew	9	2							11
First cousin	5		1		1		1	1	9
Distant	12					1			13
Total	50	5	3	1	1	1	1	1	63

[a]Involving NWTS patient and another confirmed case.
[b]Includes "probable" Wilms' tumor diagnoses.

TABLE III. Characteristic Congenital Anomalies, Gender, and Precursor Lesions*

Patient feature	Percent affected		OR	95% CI	*P* value
	Familial	Sporadic			
Number	93	6116	—	—	—
Female	49.5	53.1	0.9	0.6–1.3	0.48
Aniridia	3.2	0.7	4.8	0.9–15	0.059
Cryptorchism	5.4	2.9	1.9	0.8–6.2	0.27
BWS	3.2	0.9	3.6	0.7–11	0.12
Hemihypertrophy	5.4	3.3	1.7	0.5–4.1	0.39
ILNR only[a]	28.8	15.2	2.3	1.2–4.4	0.016
PLNR only[a]	9.6	21.3	0.4	0.1–1.0	0.046
ILNR+PLNR[a]	3.8	3.8	1.0	0.1–3.9	1.00

*BWS = Beckwith-Wiedemann syndrome; ILNR = intralobar nephrogenic rests; PLNR = perilobar nephrogenic rests.
[a]Results are based on 52 familial and 3,675 sporadic cases that were evaluable.

Congenital Anomalies and Precursor Lesions

Table III shows the association between familial Wilms' tumor and congenital anomalies and precursor lesions known to be related to Wilms' tumorigenesis. It also shows the lack of association with gender. The incidence of intralobar nephrogenic rests and aniridia is increased among the familial cases, although the latter finding is based on only three familial cases with the syndrome. Two of the three cases of aniridia occurred in the NWTSG patients from a family in which all five affected members had aniridia and Wilms' tumor arising from a balanced translocation *t* (2,11) (q32; p13) [27]. The negative association with perilobar nephrogenic rests is also of interest even if just statistically significant. Two of the three cases of Beckwith-Wiedemann syndrome occurred in NWTSG patients from one family. Another familial case arose in conjunction with the Simpson-Golabi-Behmel syndrome, an X-linked overgrowth syndrome characterized by coarse facies and visceral and skeletal anomalies [28]. No evidence was found for intrafamilial clustering of cases of the same gender or of cases that occurred in conjunction with intralobar or perilobar nephrogenic rests.

DISCUSSION

Excluding the children diagnosed with clear cell sarcoma and rhabdoid tumor of kidney, none of whom had a positive family history, we found 93 (1.5%) cases of familial disease among 6,209 patients with Wilms' tumor. In nearly half of 63 multiple-case families, there was at least one other person affected from the immediate family of the index case. By contrast, a national French study of 511 patients with Wilms' tumor found 12 (2.3%) with a positive family history, but no multiple-case nuclear families [4,14]. This difference highlights the importance of specifying the degree of relationship and of confirming diagnoses in distant relatives when estimating the incidence of familial disease. The statistical uncertainties of small samples could also affect the difference.

Judging from our results and those reported in the literature, the pattern of transmission is consistent with an autosomal dominant mutation having incomplete and possibly variable penetrance and variable expressivity [1,5,13,29]. Few instances of direct transmission from parent to child were observed (Table II), wherease multipy affected sibships were relatively common. This suggests that some cases of familial disease may result from gonadal mosaicism, a mechanism that should lead to increased observation of direct parent-child transmission in future generations, now that survivorship has improved [13]. Alternatively, this might suggest the aberrant function of an imprintor gene in the parent, such that the abnormal imprint is manifested in the child but where the primary defect in the imprintor is not necessarily inherited.

Familial Wilms' tumor is clearly heterogeneous. Epidemiologic evidence for heterogeneity stems from our observation that phenotypic characteristics, particularly bilateral involvement and the presence of metastases at diagnosis, tend to cluster in specific families. Genetic evidence comes from the observed associations of transmission or cosegregation in different families with translocation of chromosome 11p13 [27], with mutation of *WT1* [8], with the Beckwith-Wiedemann syndrome [30], and with the Simpson-Golabi-Behmel syndrome [28], as well as from the lack of linkage with any gene on chromosome 11 in other families [9–11]. The associations in Table III suggest that one or more of the genetic events leading to Wilms' tumors that occur in association with intralobar nephrogenic rests may well be heritable, whereas those leading to tumors associated with perilobar rests may not [12]. Alternatively, and perhaps more plausibly, a mutation already present in the germ cell would be early enough to generate an intralobar rest, whereas

the insult that results in a perilobar rest may occur somatically and at a later time [12].

The roughly equal number of familial cases transmitted via fathers vs. mothers, and the similarity of their respective age distributions, confirms with substantially larger numbers the results of the French study [14]. This observation conflicts with the predictions of two models of genomic imprinting in which familial cases result from transmission of a mutated tumor-suppressor gene. According to one such model, the maternal copy of a growth-promoting gene on the same chromosome as the suppressor gene is imprinted [31,32]. Another model posits mosaicism involving imprinting of the maternal copy of the suppressor gene in some cells [33]. In either case, transmission through the father would result in an increased likelihood of tumor development and an earlier age at onset [14]. Our observation that penetrance and age at onset do not depend on the gender of the transmitting parent is consistent with a third model, however, in which familial cases result from transmission of a gene that regulates the degree of imprinting and that segregates independently of the suppressor gene [34].

Earlier analyses of NWTSG data were unable to clearly distinguish the ages of the familial cases from those of other subgroups [3,35]. The larger numbers of cases now available demonstrate that the familial subgroup as a whole is younger, on average, than the sporadic subgroup. In fact, its age distribution is similar to that of the sporadic bilateral cases, just as predicted by Knudson's original two-stage model [5,6]. Quite surprising, however, is the fact that so few (16.1%) of the familial cases are bilateral and that the bilateral familial cases occur so much earlier in life than do the unilateral, familial cases and the sporadic, bilateral cases (Table I). Neither observation is consistent with the hypothesis that an inherited mutation is responsible for all bilateral cases [3,36]. Perhaps bilateral disease and earlier age at onset are simply both manifestations of increased expression of the genetic trait, whether this is inherited or acquired somatically.

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COMMENTARY

Breslow et al. report on 93 patients from 63 families with a positive family history for Wilms' tumor, demonstrating again the invaluable strength of the National Wilms' Tumor Study Group. In the largest series on familial Wilms' tumor reported thus far, the authors demonstrate for the first time that the familial subgroup as a whole is younger, on average, than the sporadic subgroup, as predicted by Knudson and Strong in 1972. Quite surprising, however, is their observation that so few of the familial cases are bilateral (a much higher incidence was predicted by the two-hit hypothesis). Of great interest is the demonstration that familial Wilms' tumor is heterogeneous. In its initial manifestation, for example, bilateral involvement and the presence of metastases at diagnosis tend to cluster in families. Finally, this manuscript confirms that the pattern of transmission in familial Wilms' tumor is consistent with an autosomal dominant mutation. In short, Breslow et al. provide interesting data that can be used by molecular biologists to readdress the genetics of familial Wilms' tumor.